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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,766	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-46 and 49-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-46 and 49-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/22/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 22 August 2006 has been entered.

Status of Application, Amendments and/or Claims

Claims 44-46 and 49-52 are under consideration in the instant application. Applicant's remarks submitted 22 August 2006 have been entered into the record. The declaration by Dr. Scott (received 22 August 2006) have been entered into the record, and is addressed below.

Information Disclosure Statement

The information disclosure statement submitted on 22 August 2006 has been fully considered.

Claim Rejections - 35 USC § 101 and 35 USC § 112, First Paragraph

Claims 44-46 and 49-52 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or

a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation to determine their utility. The basis for this rejection is of record.

Claims 44-46 and 49-52 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons of record, one skilled in the art clearly would not know how to use the claimed invention.

Specifically, claims 44-46 and 49-52 are directed to the polypeptide of SEQ ID NO: 96, the polypeptide of SEQ ID NO: 96 without the signal sequence, and the extracellular domain of the polypeptide of SEQ ID NO: 96. Claims are also presented to the polypeptide encoded by ATCC deposit 209397. Finally, claims are presented to chimeric polypeptides comprising the above polypeptides fused to a heterologous polypeptide. The specification teaches that the polypeptide of SEQ ID NO: 96, also known as PRO269, is a membrane-bound polypeptide with a single transmembrane domain. PRO269 does not have significant structural similarity to any fully characterized polypeptides. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO269 polypeptide. Without any information as to the specific properties of PRO269, the mere identification of such as being a membrane-bound polypeptide possessing a single transmembrane domain is not sufficient to impart a well-established utility to the polypeptides or the antibodies which specifically bind them. The specification contains numerous asserted utilities for

PRO269, including use as molecular weight markers, therapeutic agents, and for the production of antibodies. None of these asserted utilities is specific for the disclosed PRO269 polypeptide, as each of the aforementioned utilities could be asserted for any naturally occurring polypeptide, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO269.

Applicant has gone on record that they rely upon the gene amplification assay to establish utility and enablement for the claimed invention. See p. 4 of the Appeal Brief received 13 September 2005. At pages 222-235 of the specification, a gene amplification assay discloses that genomic DNA encoding PRO269 had a ΔCt value of at least 1.0 for eight out of seventeen lung tumor samples. Genomic DNA encoding PRO269 was not amplified in any of the seventeen colon tumor samples. The specification asserts that amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers. However, the art shows that amplification data for genomic DNA have no bearing on the utility of the encoded polypeptides. In order for PRO269 polypeptides to be overexpressed in lung tumors, amplified genomic DNA would have to correlate with amplified mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed. Regarding the correlation between genomic DNA amplification and increased mRNA expression, see Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Even if increased mRNA levels could be established for PRO269, it does not follow that polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation

between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977).

The art also shows that mRNA (transcript) levels do not correlate with polypeptide levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 polypeptides. They concluded that

> "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein

> expression and reveal that simple deduction from mRNA transcript analysis is insufficient"

(See Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may

differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood.

Therefore, data pertaining to PRO269 genomic DNA do not indicate anything significant regarding the claimed PRO269 polypeptides. The data do not support the specification's assertion that PRO269 polypeptides can be used as a cancer diagnostic agent or as a therapeutic drug development target. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO269 polypeptide is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent or therapeutic drug development target, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO269 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO269 **polypeptides or antibodies** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful

conclusion."

Applicant's arguments (22 August 2006), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant argues that they are not required to establish overexpression in a majority of tumors. Applicant urges that markers for rare tumors are valuable. Finally, Applicant argues that they have shown an overexpression in lung tumors but not colon tumors, which is useful. This has been fully considered but is not found to be persuasive. The specification does not disclose a rare type of tumor that can be diagnosed with PRO269 biological molecules. If a skilled artisan used a PRO269 genomic DNA probe on a new lung sample and there was no amplification, no diagnosis could be made since PRO269 was amplified in some known lung tumors and not amplified in other known lung tumors. The specification asserts that PRO269 polypeptides are elevated in tumor tissues based on gene amplification results; however, the literature evidences that this assumption is a false one. The claims are directed to PRO269 antibodies which can only detect differences in protein levels. As argued on the record, the gene amplification data for PRO269 genomic DNA do not impart utility to the PRO269 polypeptides or antibodies because amplification of DNA is not predictive of increased mRNA levels and increased polypeptide levels. Regarding rare tumor markers, such rare tumor markers are only useful if the type of rare tumor it identifies is known. The specification has not identified anything rare, or anything in

common, among the lung tumor samples in which the PRO269 gene is amplified. PRO269 gene tested positive in LT7, LT13, LT9, LT12, LT11, LT15, LT17, and LT19 samples. Table 8 identifies these samples as lung squamous cell carcinomas, adenocarcinomas, and mixed tumors of various stages.

Applicant argues that the examiner improperly disregarded the Goddard declaration. Applicant urges that the Goddard declaration and the Orntoft et al. publication serve as evidence that two fold amplification is significant. This has been fully considered but is not found to be persuasive. The Goddard declaration has been considered as well as all of the other evidence of record. See pp. 4-5 of the final rejection mailed 21 April 2006, for example. All of the evidence has been considered anew each time the application has come before the examiner for action. The rejection is being maintained based on the preponderance of the totality of the evidence.

From p. 4 to p. 12 of the remarks received 22 August 2006, Applicant takes issue with Pennica et al., Konopka et al., Hu et al., LaBaer, Chen et al., Hanna and Mornin, Haynes et al., Gygi et al., Lian et al., Fessler et al., and Greenbaum et al. Applicant relies on Orntoft et al., Hyman et al., Pollack et al. and Futcher et al. as supporting their position. This has been fully considered but is not found to be persuasive. Hu et al., Haynes et al., and Hanna and Mornin have already been discussed fully on the record. Pennica et al. and Konopka et al. constitute evidence that gene amplification is not predictive of increased mRNA levels. Applicant's criticism of Hu et al. and LaBaer for using faulty statistical analysis is not fatal to the rejection. Hu et al. and LaBaer were published in peer-reviewed journals, so it cannot be alleged that they are scientifically

deficient. Even if, *arguendo*, Hu et al.'s and LaBaer's statistical analysis was not sufficiently stringent, the instant application provides no statistical analysis, and thus Applicant is holding Hu et al. and LaBaer to a higher standard than their own disclosure. The arguments with regard to Chen et al. are duplicative of those of record; thus Chen et al continues to be relied upon for reasons of record. Applicant quotes from Beer et al.; however, the quoted passage is relevant to whether or not oligonucleotide microarrays are predictive of mRNA levels *in situ,* and NOT whether gene amplification is predictive of increased mRNA, or is increased mRNA is predictive of increased polypeptide levels. Applicant's argument that Gygi et al. are focussed on accuracy and thus is not relevant is not persuasive because the reference clearly shows that protein levels cannot be predicted from mRNA levels. Applicant's arguments concerning Lian et al. and Fessler et al. are substantially duplicative of those of record and thus are not persuasive for reasons of record. Regarding Greenbaum et al., Applicant quotes from a passage that is relevant to highly expressed ORFs. There is no evidence that PRO269 is a highly expressed ORF. Greenbaum et al. establishes that polypeptide levels are controlled at several points and cautions against relying on mRNA levels to predict polypeptide levels.

Applicant also asserts that Futcher et al. (1999) conducted a study of mRNA and protein expression in yeast and report a good correlation between protein abundance and mRNA abundance. Applicant's arguments have been fully considered but are not found to be persuasive. Futcher et al concludes that "[t]his validates the use of mRNA abundance as a rough predictor of protein abundance, at least for relatively abundant

proteins [emphasis added]" (pg 7368, col 1). There is no evidence that PRO269 is such a protein. Futcher et al. also admits that Gygi et al. performed a similar study and generated similar data, but reached a different conclusion. Futcher et al. indicates that "Gygi et al. feel that mRNA abundance is a poor predictor of protein abundance" (pg 7367, col 1, 1st full paragraph).

Applicant discusses the Polakis I declaration. This was discussed in the examiner's answer:

> In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO269 (i.e., data regarding amplification of PRO269 genomic DNA), and does not disclose any information regarding PRO269 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Konopka et al., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., and Greenbaum et al., all discussed *supra*. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

Applicant presents and discusses a second declaration by Dr. Polakis, submitted with the response on 30 March 2006. Applicant argues that this declaration provides the facts, set forth in a table (Exhibit B), for independent evaluation by the Examiner. The second Polakis declaration under 37 CFR § 1.132 filed 30 March 2006 is insufficient to overcome the rejection of claims 44-46 and 49-52 based upon 25 U.S.C. §§ 101 and 112, first paragraph, for the following reasons. Specifically, data for PRO269 does not appear in the table (Exhibit B). Furthermore, it is not clear how the clones appearing in the table compare to PRO269, or if the results presented in the table were determined by the same methodology as presented in Example 30 of the instant specification. For example, how highly expressed were the genes in Exhibit B that purportedly correlate with increased protein levels, 2-fold, 5-fold, 10-fold? How many samples were used? By what means was the level of mRNA expression determined, e.g., microarray, Northern blot, quantitative PCR? Was the "universal normal control" used or were matched tissue controls used? The declaration only states that levels of mRNA and protein in tumor tissue were compared to normal tissue.

Applicant refer to another declaration by Dr. Scott, submitted with the response on 22 August 2006. Applicant argues that Dr. Scott, an eminent researcher in this field, is of the opinion that mRNA levels correlate with protein levels. The Scott declaration under 37 CFR 1.132 filed 22 August 2006 is insufficient to overcome the rejection of claims 44-46 and 49-52 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1)

the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, (1) the nature of the fact sought to be established is whether or not mRNA levels are predictive of polypeptide levels in a sample. (2) The opposing evidence, cited by the examiner, is considerably strong. Please see the numerous references cited above, including Chen et al. and Greenbaum et al. (3) Dr. Scott does not appear to have an interest in the outcome of the case. (4) Finally, the Dr. Scott does not base his opinion an any particular facts other than his own considerable experience in the field. Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949). While the declaration constitutes evidence that must be considered, there is also other evidence that mRNA levels are not predictive of polypeptide levels. The mere volume of contradictory publications on this topic speaks to the unpredictability of the issue. Also, there remains the issue of the universal normal control used in the microarray assay of this specification. Thus, consideration of the preponderance of the totality of the evidence indicates that the rejections should be maintained.

Applicant has submitted teachings from Alberts, B. (Molecular Biology of the Cell (3rd ed 1994 and 4th ed 2002)) and Lewin, B. (Genes VI 1997) to support the statements

of Dr. Polakis (Polakis II declaration). Applicant also cites numerous references to emphasize that those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression (such as Zhigang et al., Meric et al. Orntoft et al., Wang et al., Munaut et al., etc.). Applicant asserts that changes in mRNA level generally lead to corresponding changes in the level of expressed protein. Applicant also contends that the references and the Polakis declaration establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Applicant's arguments have been fully considered but are not found to be persuasive. While the Examiner acknowledges the teachings of Alberts and Lewin, which disclose that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (see Alberts 3rd ed., bottom of pg 453). Meric et al. states the following: "The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription."

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974). Celis et al. also teach that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (pg 6, col 2).

Furthermore, with the exception of Futcher et al., all of Applicant's newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. The studies cited by Applicant that examine the expression of specific genes or small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined and more accurately describe general trends, specifically, Haynes (80 proteins examined) and Chen (165 proteins examined) (cited previously by Examiner) and Nagaraja et al. (2006), Waghray et al. (2001) and Sagynaliev et al. (2006) (described below).

With regard to the Orntoft reference, Applicants submit that Orntoft examined 40 well-resolved abundant proteins, and found significant correlation between mRNA and protein alterations (including both increases and decreases) for each gene, except one.

Applicants' arguments with respect to Orntoft have been fully considered but are not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and compare that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). This analysis was not done for PRO269 in the instant specification. That is, it is not clear whether or not PRO269 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Orntoft et al. is not clear.

The Examiner maintains the previous argument that mRNA levels are not necessarily predictive of protein levels, and in response to Applicants' arguments, maintains that this is true even when there is a change in the mRNA level. Comprehensive studies where significantly large numbers of transcripts and proteins were examined report that increases in mRNA and protein samples are not correlated. Nagaraja et al. (Oncogene, 25:2328-2338, 2006) characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231 and report that "the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles" (see abstract), and "the comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in

the microarray designated profiles and vice versa" (see pg 2329, first column). Nagaraja et al. further report that, "a comparative analysis of transcripts and proteins to establish a relationship between transcript changes and protein levels has not yet become routine" (see pg 2328, second column). Lastly, Nagaraja et al. report that, "as dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles" (see pg 2335, first column).

Similar results were reported by Waghray et al. (Proteomics, 1:1327-1338, 2001). Waghray et al. analyzed gene expression changes induced by dihydrostesterone (DHT) in the androgen responsive cancer line LNCaP, at both RNA and protein levels (see abstract). In this study, Waghray et al identified transcripts from 16750 genes and found 351 genes were significantly altered by DHT treatment and the RNA level, and identified 1031 proteins and found 44 protein spots that changed in intensity (either increased or decreased). Out of the 44 protein spots that changed in intensity, Waghray et al. reports that, "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level" (see pg 1333-1334, Table 4). Waghray et al. clearly state that, "The change in intensity for most of the affected proteins identified could not be predicted based on the level of the corresponding RNA" (see abstract).

In a review of gene expression in colorectal cancer (CRC), Sagynaliev et al. (Proteomics, 5:3066-3078, 2005) report that "it is also difficult to reproduce transcriptomics results with proteomics tools. Out of 982 genes found to be differentially

expressed in human CRC by genome-wide transcriptomics technologies (Table 6a), only 177 (18%) have been confirmed using proteomics technologies" (see pg 3068). In summary, it is clear that Nagaraja, Waghray and Sagynaliev support the Examiner's position that changes in mRNA expression frequently do not result in changes in protein expression. It is also noted that the specification of the instant application does not teach a change in mRNA level of PRO269. The specification simply discloses a static measurement of PRO269 mRNA in lung tumor as compared to a universal control. There are no teachings in the specification as to the differential expression of PRO269 mRNA in the progression of lung cancer or in response to different treatments of hormones (for example). Therefore, the Examiner maintains that Applicant's measurement of an increase of PRO269 mRNA does not provide a specific and substantial utility for the encoded protein, or an antibody to the protein.

The state of the art, as evidenced through textbooks and review papers, clearly establishes that polypeptide levels cannot be accurately predicted from mRNA levels. Lilley et al. teach that "DNA chips (mRNA profiling studies) can contribute to the study of gene expression in response to a particular biological perturbation. However, the extrapolation that changes in transcript level will also result in corresponding changes in protein amount or activity cannot always be made" ("Proteomics" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, page 351). Wildsmith et al. also disclose that the gene expression data obtained from a microarray may differ from protein expression data ("Gene Expression Analysis Using Microarrays" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, pages 269-286,

especially pg 283). King et al. disclose that "it has been established that mRNA levels do not necessarily correlate with protein levels" (pg 2287, 2nd full paragraph). King et al. state that it has been demonstrated that correlation between mRNA and protein abundance is less than 0.5 and that "mRNA expression studies should be accompanied by analyses at the protein level" (pg 2287, bottom of col 1 through the top of col 2; see also Bork et al., Genome Res 398-400, 2000, especially pg 398, bottom of col 3). Haynes et al. teach that "[p]rotein expression levels are not predictable from the mRNA expression levels" (pg 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (pg 1870, under concluding remarks). Madoz-Gurpide et al. disclose that "[f]or most of the published studies it is unclear how well RNA levels reported correlate with protein levels" (pg 53, 1st full paragraph). However, the specification of the instant application has only disclosed that the PRO269 polynucleotide is overexpressed in lung tumor. The specification does not indicate that the PRO269 polypeptide has been overexpressed in the lung tumor sample tested. Given the asserted increase in PRO269 expression, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that an increase in mRNA expression would correlate with significantly increased polypeptide levels. Further research needs to be done to determine whether the purported increase in PRO269 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not

substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
"a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the specification's assertions that the PRO269 polypeptides have utility in the fields of cancer diagnostics is not substantial.

Additionally, the majority of the newly cited references by Applicants are drawn to genes known or suspected to be over expressed or under expressed in cancers, and that are involved with cell proliferation, differentiation and/or cell adhesion/migration, in which expression of the protein is important in the development and progression of the cancer. For example, Wang et al. analyzes expression of the cadherins, which are a family of transmembrane proteins that play a crucial role in cell differentiation, cell migration, and intercellular adhesion. Down-regulation of E-cadherin protein had been shown in various human cancers. Wang et al. states: "In conclusion, this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied. This down-regulation may play an important role in the pathogenesis of prostate cancer." Maruyama et al. studied the expression of Id proteins. Id proteins antagonize basic helix-loop-helix proteins, inhibit differentiation, and enhance cell proliferation. In their

study they compared the expression of Id-I, Id-2, and Id-3 in the normal pancreas, in pancreatic cancer, and in chronic pancreatitis (CP), and found increases in both mRNA and protein compared to normal. Maruyama et al. state: "These findings suggest that increased Id expression may be associated with enhanced proliferative potential of pancreatic cancer cells and of proliferating or dysplastic ductal cells in CP."

Munaut et al. teach that vascular endothelial growth factor (VEGF) is the major endothelial mitogen in central nervous system neoplasms and it is expressed in 64-95% of glioblastomas (GBMs). Munaut et al. state "Tumour cells are the main source of VEGF in GBMs whereas VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial ceils. Infiltrating tumour cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinase's (MMPs). Recent studies have shown that VEGF expression and bioavailability can be modulated by MMPs. We reported previously that the expression of MTI-MMP in human breast cancer cells was associated with an enhanced VEGF expression.....Our results suggest that the interplay between metalloproteinase's and VEGF previously described in experimental tumours may also be operative in human GBMs. Because of its dual ability to activate MMP-2 and. to up-regulate VEGF, MTI-MMP might be of central importance in the growth of GBMs and represent an interesting target for anti-cancer treatments."

Rudlowski et al. (cited in IDS filed August 22, 2006), examined GLUT1 mRNA and protein induction in malignant transformation of cervical cancer. The authors state: "We studied whether induction of glucose transporters (GLUTs) 1 to 4 correlates with

human papillomavirus (HPV)-dependent malignant transformation of cervical epithelium. Tissue samples of cervical intraepithelial neoplasia (CIN; grades 1 to 3), invasive carcinomas, and lymph node metastasis were examined. HPV typing was performed. In CIN 3 high-risk HPV lesions, cervical cancer, and metastasis, GLUT1 was expressed at highest levels with a strong correlation of GLUT1 mRNA and protein expression. Immunostains for GLUT2 to GLUT4 were negative. Cervical tumour cells respond to enhanced glucose utilization by up-regulation of GLUTI. The strong induction of GLUTI mRNA and protein in HPV-positive CIN 3 lesions suggests GLUTI over expression as an early event in cervical neoplasia. GLUTI is potentially relevant as a diagnostic tool and glucose metabolism as a therapeutic target in cervical cancer. "

Bea et al. (cited in IDS filed 22 August 2006) studied gene amplification, mRNA expression and protein expression of the BMI-1 gene, which is a putative oncogene belonging to the Polycomb group family that cooperates with c-myc in the generation of mouse lymphomas and seems to participate in cell cycle regulation and senescence by acting as a transcriptional repressor of the INK4a/AILF locus. Bea et al. reported that four tumours with gene amplification showed significantly higher mRNA levels and significantly higher protein expression than other MCLs and NHLs with the BMI-1 germ line configuration. Applicants assert that Bea et al. supports the assertion that gene amplification is correlated with both increased mRNA and protein expression. However, as discussed above, it is not unexpected that a putative oncogene that seems to participate in cell cycle regulation and senescence, when amplified in the genome, would also be amplified as mRNA and have correspondingly increased protein

expression. PRO269 is not a putative oncogene, and the function of the encoded protein is not known.

While the vast majority of newly cited references are drawn to predictability of protein on the basis of mRNA amplification, a single reference, that by Godbout, is pertinent to the issue at hand. Far from teaching predictability for expression of PRO269 on the basis of a minor genomic amplification, the abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell* (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first

three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons."

On the contrary, there is no structure/function analysis in the specification regarding the putative protein encoded by the PRO269 gene. It is not disclosed, and based upon the sequence searches in this case, the Examiner can not find any reason to suspect, that the protein encoded by the PRO269 gene would confer any selective advantage on a cell expressing it. It has no known homology to an RNA helicase or any other protein that would be expected to confer a selective advantage to a tumor cell. Further, it cannot be determined from the abstract whether the level of genomic amplification of the DDX1 gene was comparable to that disclosed for PRO269.

In summary, of applicants' 140 references submitted, only a single one, Godbout, is drawn to the predictability of protein levels based upon genomic DNA amplification, and that one supports the Examiners assertion that it is more likely than not that the PRO269 protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no utility as a cancer diagnostic.

An additional reference that provides evidence that gene amplification does not necessarily lead to increased transcript is Li et al., Oncogene, Vol. 25, pages 2628-2635, 2006. Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "*In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels*, implying that at least some of these genes are

'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*."

In view of the preponderance of the totality of the evidence, the rejections are deemed proper and are maintained.

Conclusion

No claims are allowable.

This is a continuation of applicant's earlier Application No. 09/904,766. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Applicant is advised that the instant rejection was made final because the same claims were maintained as rejected on the same grounds that have been of record. However, new references have been cited as evidence supporting the rejections of record. Applicant may submit counter-evidence in response to this office action, which will be appropriately entered after final. Alternatively, Applicant may wish to submit an Appeal Brief in response to this office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ECK

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER